CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75203

MEDICAL REVIEW

Medical Officer Review
January 21, 2000

Drug Product: Propafenone Hydrochloride Tablets
Sponsor: Watson Laboratories, Inc.

Issue: Reference Listed Drug dosage

Background

Watson Laboratories submitted a fasting pharmacokinetic study using the 300mg dose originally. This study failed to demonstrate bioequivalence. Before the review was completed on this study, they submitted a controlled document requesting that the food study be conducted on the 225mg dose for potential safety reasons. They cited electrocardiogram T-wave changes in subjects receiving 300mg in the fasting study as well as a paper that reported a marked enhancement in AUC when the drug was administered with food (mean increase of 120% with one individual with a rise of 682%). They were permitted to use the lower dose of 225mg for the food study. When they were notified that the 300mg fasting study had failed, they interpreted the letter approving use of the lower dose as indicating that both fasting and non-fasting studies should be done using the same dose and repeated their fasting study on the 225mg dose. The issue of the Reference Listed Drug dosage is the subject of this review.

Review of Adverse Event Reporting

The occurrence of adverse events (ADEs) in the 300mg fasting study is summarized in the attached table. Eighteen ADEs were reported in 6 subjects. Six occurred after subjects received the test drug and 12 occurred on the reference drug. One subject experienced 8 ADEs, 5 on reference drug and 3 on test; one subject reported 5 ADEs, 1 on test and 4 on reference drug. Of the 18 ADES, only 5 were determined to be "possibly related" to drug. These included dizziness (2), nausea (1), lightheadedness (1), and syncope (1). Among those reported as "unlikely" to be due to drug, 8 were headaches, and 1 was hot flashes. Headache and flu symptoms that preceded the ingestion of drug, and congestion and phlebitis were determined to be "unrelated" to study drug.

The electrocardiograms of the subjects were reviewed carefully. Minor ST changes were noted and included ST elevation which appeared to be early re-polarization as well as minor changes in the T-u wave conformation. These changes were present at the baseline EKG and were more visible in some subsequent EKGs. However, they were not apparently enhanced by drug administration.

The studies reported in the PDR indicate that propafenone prolongs A-V conduction with little to no effect on sinus node function. A-V nodal conduction time and His-Purkinje conduction time are prolonged. It slows conduction and therefore produced dose related changes in the PR interval and QRS duration. The QTc interval does not change..

The clinical trials reported indicate that dose related increases are seen in the most common ADEs. These are shown in the following table.

	Ventricular Arrhythmia patients				SVT patients		Ventricular Arrhythmia patients
	450mg/d (150mg)	600mg/d (225mg)	>/=900mg /d (300mg)	% who discontinued Rx		% who discontinued Rx	
ADE	N=1430	N=1337	N=1333		N=480		N=247
Dizziness	4%	7%	11%	2.4%	9%	1.7%	7%
Nausea	2%	6%	9%	3.4%	11%	2.9%	3%
Unusual taste	3%	5%	6%	0.7%	14%	1.3%	7%
Headache	2%	2%	3%	0.5%	6%	0.8%	5%

Reports of cardiac ADEs occur at a low level as noted below. While there is some trend to increase with dose these are still at a low level at the highest dose. None of these ADEs are related to changes in the ST segments or T waves.

	Ventricular Arrhythmia patients				SVT patients		Ventricular Arrhythmia patients
	450mg/d (150mg)	600mg/d (225mg)	>/=900mg /d (300mg)	% who discontinued Rx		% who discontinued Rx	
ADE	N=1430	N=1337	N=1333		N=480		N=247
AV block first degree	1%	1%	2%	0.3%	0%	0%	5%
QRS duration, increased	1%	1%	2%	0.5%	0%	0%	0%
Bradycardia	1%	1%	1%	0.5%	2%	0.2%	0%
Bundle branch block	0%	1%	1%	0.5%	0%	0%	1%

Conclusion

There were no safety issues identified during the initial fasting 300mg study. The potential for some increase in AUC that might occur during a fed study does not raise any additional safety concerns. Both the fasting and fed studies should be conducted at the 300 mg dose.

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